

REMARKS

With the entry of this amendment, claims 33-52 are pending. Claim 33 is amended herein. The amendments add no new matter.

Formalities:

Specification:

The specification is objected to because the text is not clearly visible on, e.g., pages 10, 12, 20, 22, 30, 32, 34, 42, 44 and 46. The Office Action requested a substitute specification with clearer text. Applicants submit herewith a Substitute Specification and request its entry. Applicants submit that the Substitute Specification is identical in content to that originally filed, and that no new matter is added. Applicants note that the Substitute Specification includes the claims as originally filed (on pages 50-52) before the Abstract on page 53 – Applicants wish to emphasize that the claims to be currently considered are those in the “Listing of the Claims” beginning on page 3 of this response.

Figures:

The Office Action notes that the application was filed with informal figures and that formal figures will be required when the application is allowed. Applicants will submit formal figures upon allowance of the claims.

Rejection under 35 U.S.C. §112, Second Paragraph:

Claims 33-52 are rejected as indefinite under 35 U.S.C. §112, second paragraph.

The Office Action states that claim 33 is indefinite for recitation of “a method for selecting a binding polypeptide from a repertoire of polypeptides..... comprising the steps of a) contacting the repertoire with the generic ligand to select polypeptides bound thereto...., b) contacting the selected pool of polypeptides with target ligand to select a population of polypeptides which bind to the target ligand.’ In the claimed method it is not clear whether the first selected pool of binding polypeptides are still bound to the generic ligand such that the

target ligand binds to a different binding site. That is it is not clear whether the target binding site and ligand binding site are different from each other.” Applicants respectfully disagree.

Applicants submit that claim 33 recites in part “a method of selecting a binding polypeptide from a repertoire of polypeptides, the binding polypeptide comprising a first, target binding site and a second, generic ligand binding site.” That is, the claim makes it clear that the binding polypeptide to be selected has a first site that binds a target ligand and a second site that binds a generic ligand. In view of this, Applicants submit that it is irrelevant whether or not the first selected pool of binding polypeptides is still bound to the generic ligand when the first selected pool is contacted with the target ligand, because the claim requires that a population in the first selected pool of polypeptides (selected for binding to the generic ligand) has a site that binds the target ligand.

The Office Action requests that in claim 33, step (b), the phrase “the first selected pool of polypeptides” be amended to recite “the first selected pool of *binding* polypeptides.” Applicants submit that the phrase is unambiguous as written, in that it clearly refers to the only “first selected pool” previously referred to in the claim, which is that referred to in step (a). Nonetheless, in the interest of advancing prosecution, Applicants have amended step (b) to recite “the first selected pool of binding polypeptides.” Because the antecedent basis for the term is clear in the claim as written, Applicants submit that this amendment is not made for a reason pertinent to patentability.

The Office Action states that the amendment of claims 33 and 52 to add commas after “first” and “second” seems to be a grammatical error and requests that it be corrected.

Applicants respectfully disagree.

Applicants submit that the commas after “first” and “second” are grammatically correct, in that they separate two adjectives in a row that modify the same noun. Thus, the term “binding site” is modified by both the adjective “first” and the adjective “target”, and the term “ligand binding site” is modified by the adjectives “second” and “generic.” The commas were added in order to clarify confusion apparent from the remarks in the Restriction Requirement with regard to how many generic ligand binding sites are present on the recited binding polypeptide. The

Restriction Requirement mailed February 13, 2003 had a species election requirements phrased as follows:

“d) a single species of second generic ligand (if it is different from generic ligand). Note that claims 33 and 52 recite a second generic ligand, it may be same or different from the generic ligand.”

Applicants submit that there are only two binding sites required by either of claims 33 or 52: one target ligand binding site (referred to as the “first, target binding site”) and *one* generic ligand binding site (referred to as the “second, generic ligand binding site.”) The commas were added to make it clear that there are not two generic ligand binding sites, but one, referred to as the “second, generic ligand binding site” to distinguish it from the “first, target ligand binding site.” Applicants have therefore not amended the commas out of claims 33 and 52 as previously amended.

Rejection under 35 U.S.C. §102(e):

Claims 33-41 and 44-52 are rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 6,057,098 (Buechler et al.).

Applicants submit that Buechler et al. is not prior art over the present application. The accompanying Rule 131 Declarations of both inventors Ian M. Tomlinson and Greg P. Winter, the entire inventive entity, establish a date of conception prior to the April 4, 1997 effective date of the ‘098 reference, with subsequent diligence in reduction to practice.

Dr. Tomlinson states in the accompanying Declaration under 37 C.F.R. §1.131 that, prior to April 4, 1997, he and co-inventor Winter together conceived an approach to overcome the problems in phage display library screening approaches caused by a high background of non-folded or improperly folded library members resulting from the introduction of diversity. Dr. Tomlinson states that in this approach, a sub-library of antibody Heavy chains is selected for members that properly fold, a sub library of Light chains is selected for members that properly fold, and the two selected sub-libraries are combined to form a library of antibodies that have been pre-selected for folded members that is then selected for binding to target antigen. The pre-selection for proper folding is performed by binding the members of each sub-library to a generic ligand that only binds properly folded sub-library molecules. The population of library members

that binds the generic ligand was subsequently selected for binding to several different target ligands. Applicants submit that this approach satisfies the limitations of claim 1, from which all other claims ultimately depend.

Dr. Tomlinson's Declaration is accompanied by copies of his notebook pages documenting the conception of the claimed invention and the subsequent diligent efforts culminating in an actual reduction to practice.

Dr. Winter states in his Rule 131 Declaration that prior to April 4, 1997, he and Dr. Tomlinson had conceived of the claimed invention. Specifically, he states that he and Dr. Tomlinson had "had discussions on several occasions prior to April 4, 1997 regarding ways to improve polypeptide library technology." He continues, stating that

"we discussed the problems posed by the presence of a large background of library members that, due to the means used to introduce diversity (typically degenerate oligonucleotides and PCR), are not capable of proper folding and are therefore non-functional for binding to any target molecule. We recognized that a selection of library members for those capable of folding into a functional conformation would increase the likelihood of identifying library members that bind a desired target ligand."

Dr. Winter continues by describing the joint conception, through these discussions, of a method in which functional members of a library could be selected by selecting members of a library that bind a ligand generic to all members of the library, where proper folding is required for binding to the generic ligand. He states that "selection for binding to such a generic ligand would increase the proportion of molecules potentially in a conformation capable of binding a desired target," and that "selection performed on the resulting enriched library can identify functional members that also bind a desired target ligand." He further states:

"Thus, we had conceived of an approach for selecting a functional polypeptide library member from a repertoire comprising functional and non-functional members by selecting the repertoire with a generic ligand that only binds functional members, and then selecting the resulting pool of functional members for binding to a target ligand."

Dr. Winter's declaration further outlines the issues that he and Dr. Tomlinson considered in designing a library on which to demonstrate the new method, and the issues considered in the actual reduction to practice carried out by Dr. Tomlinson in consultation with Dr. Winter. Dr.

Winter states that he has reviewed the notebook pages contained in Dr. Tomlinson's declaration and fully concurs that their discussions and Dr. Tomlinson's experimental work are in accord with both the notebook entries and with Dr. Tomlinson's statements in his declaration. As noted above, the notebook pages demonstrate a reduction to practice of a method satisfying the limitations of claim 1.

In view of the Rule 131 declarations by the entire inventive entity setting forth conception prior to the April 4, 1997 date of the '098 reference, and subsequent diligence in reduction to practice for a method satisfying the limitations of claim 1, Applicants submit that the '098 reference is not prior art over the claimed invention. Applicants respectfully request the withdrawal of the §102 rejections of the present claims over the '098 reference.

Obviousness-type Double Patenting:

Claims 33-52 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5-14 and 36-44 of copending Application No. 09/192,854.

Applicants submit herewith a terminal disclaimer, disclaiming patent term for a patent issuing from this application that would extend beyond the patent term of the patent issuing from Application No. 09/192,854. Applicants submit that the terminal disclaimer is sufficient to overcome this ground of rejection.

In view of the above, Applicants submit that all issues raised in the Office Action have been addressed herein and that the claims are in condition for allowance. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

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